CLAIM AMENDMENTS

1-20. (Canceled)

21. (Currently Amended-Withdrawn) An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of SEQ ID NO:120,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:120, and

c) ~~a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:120, and~~

~~d)~~ an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:120, wherein said fragment comprises at least ~~5~~ 10 contiguous amino acid residues of SEQ ID NO:120.

22. (Currently Amended-Withdrawn) The ~~An~~ isolated polypeptide of claim 21 comprising the ~~an~~ amino acid sequence of SEQ ID NO:120.

23. (Withdrawn) An isolated polynucleotide encoding a polypeptide of claim 21.

24. (Currently Amended-Withdrawn) An isolated polynucleotide encoding the ~~a~~ polypeptide of claim 22.

25. (Currently Amended-Withdrawn) The ~~An~~ isolated polynucleotide of claim 24 comprising a polynucleotide sequence of SEQ ID NO:254.

26. (Withdrawn) A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 23.

27. (Withdrawn) A cell transformed with a recombinant polynucleotide of claim 26.

28. (Withdrawn) A method of producing a polypeptide of claim 21, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 21, and

b) recovering the polypeptide so expressed.

29. (Currently Amended-Withdrawn) The ~~A~~ method of claim 28, wherein the polypeptide comprises the ~~an~~ amino acid sequence of SEQ ID NO:120.

30. (Previously Presented) An isolated antibody which specifically binds to a polypeptide of claim 21.

31. (Withdrawn) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:254,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:254,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

32. (Withdrawn) An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 31.

33. (Previously Presented) A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 31, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

34. (Previously Presented) A method of claim 33, wherein the probe comprises at least 60 contiguous nucleotides.

35. (Previously Presented) A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 31, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

36. (Withdrawn) A composition comprising a polypeptide of claim 21 and a pharmaceutically acceptable excipient.

37. (Currently Amended-Withdrawn) The ~~A~~ composition of claim 36, wherein the polypeptide comprises the ~~an~~ amino acid sequence of SEQ ID NO:120.

38. (Currently Amended-Withdrawn) A method for treating a disease or condition associated with decreased expression of ~~functional HSPP~~ a polypeptide of claim 21, comprising administering to a patient in need of such treatment ~~the~~ a composition ~~of claim 36~~ comprising a polypeptide of claim 21 and a pharmaceutically acceptable excipient.

39. (Previously Presented) A method of screening for a compound that specifically binds to the polypeptide of claim 21, the method comprising:

a) combining the polypeptide of claim 21 with at least one test compound under suitable conditions, and

b) detecting binding of the polypeptide of claim 21 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 21.

40. (Previously Presented) A method of screening for a compound that modulates the activity of the polypeptide of claim 21, the method comprising:

a) combining the polypeptide of claim 21 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 21,

b) assessing the activity of the polypeptide of claim 21 in the presence of the test compound, and

c) comparing the activity of the polypeptide of claim 21 in the presence of the test compound with the activity of the polypeptide of claim 21 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 21 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 21.

41. (Previously Presented) A method of screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 25, the method comprising:

a) contacting a sample comprising the target polynucleotide with a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

42. (Previously Presented) A method of screening for potential toxicity of a test compound, the method comprising:

a) treating a biological sample containing nucleic acids with the test compound,

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 31 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 31 or fragment thereof,

c) quantifying the amount of hybridization complex, and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample indicates potential toxicity of the test compound.

43. (Previously Presented) A microarray wherein at least one element of the microarray is a polynucleotide of claim 32.

44. (Previously Presented) A method of generating an expression profile of a sample which contains polynucleotides, the method comprising:

a) labeling the polynucleotides of the sample,

b) contacting the elements of the microarray of claim 43 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and

c) quantifying the expression of the polynucleotides in the sample.

REMARKS

Claims 21-44 are pending in the application. Claims 21-29, 31, 32, and 36-38 are under consideration. (These claims correspond to elected Group 1. The Examiner mistakenly states on the Office Action Summary page that these claims are withdrawn from consideration.) Claims 21, 22, 24, 25, 29, 37, and 38 have been amended to further clarify the intended subject matter of the claimed invention. Entry of these amendments is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Rejoinder Request

Applicants affirm the election with traverse of claims 21-29, 31, 32, and 36-38, corresponding to the invention of Group I, drawn to polypeptides, polynucleotides, vectors, host cells, methods of making polypeptides, and methods for treating a disorder using a polypeptide. Claims 33-35 (Group II) and claims 41-42, which are drawn to methods of using the elected polynucleotides, and claims 39 and 40, which are drawn to methods of using the elected polypeptides are "method of use" claims that depend from the elected product claims of Group I. Therefore, upon allowance of the polynucleotide and polypeptide product claims of Group I, it is believed that claims 30, 33, 35, 44, and 45 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C.§ 103(b)."

Information Disclosure Statement

Applicants have submitted a new PTO-1449 form, revised as suggested by the Examiner, to include dates of submission to either the GenBank or EMBL sequence databases.

Priority Claim

The priority claim has been amended as suggested by the Examiner to include a claim to priority to PCT/US99/14484. Therefore, withdrawal of the objection to the specification is respectfully requested.

Claim Objections

The Examiner has objected to the use of an indefinite article instead of "the" in claims 22-29, 32, 36, and 33. Applicants have amended claims 22, 24, 25, 29, and 37 accordingly as requested by the Examiner. However, Applicants believe the use of an indefinite article is appropriate in claims 23, 26, 27, and 28, which refer to a polypeptide selected from alternatives of the Markush group of independent claim 21. Similarly, the indefinite article is appropriate in claim 32, which refers to a polynucleotide selected from alternatives of the Markush group of claim 31. Withdrawal of the objections to the claims is respectfully requested.

Utility Rejections under 35 U.S.C. §101 and §112, First Paragraph

Claims 21-29, 31, 32, and 36-38 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The Office Action alleges in particular that "the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well established utility" (Office Action, page 3). Applicants respectfully traverse the rejections.

The rejection of claims 21-29, 31, 32, and 36-38 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue comprises polynucleotides expressed in reproductive, nervous system, and developmental tissues and with tissues associated with cell proliferation, inflammation, or trauma (Table 3). The invention also comprises polypeptides encoded by the claimed polynucleotides. The claimed polypeptides are identified in the patent application as human signal peptide-containing proteins, abbreviated as HSPP. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this paper the Declarations of Bedilion and Furness describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:120-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, inflammation, and developmental disorders for such purposes as evaluating their efficacy and toxicity.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate. (Furness Declaration at ¶ [11]).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not

convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Uses of the claimed polypeptides and polynucleotides for diagnosis of conditions and disorders characterized by expression of HSPP, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration and the Furness Declaration accompanying this paper. Objective

evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of HSPP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration and Furness Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed polynucleotide is in fact a useful tool in cDNA microarrays used to perform gene expression analysis and that the claimed polypeptide is a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity. These uses are sufficient to establish utilities for the claimed polynucleotide and polypeptide, respectively.

The instant application is the National Stage of International Application No. PCT/US99/14484, filed on June 25, 1999, which claims priority to United States Provisional Patent Application Serial No. 60/112,129, filed on December 11, 1998 (hereinafter "the Tang '129 application").

1. The Bedilion Declaration

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Tang '129 application on December 11, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[1]

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Tang '129 specification, that the claimed polynucleotide would be useful

In connection with his explanations, Dr. Bedilion states that the "Tang '129 specification would have led a person skilled in the art on December 11, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, inflammation, and developmental disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:120-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:120-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on December 11, 1998] that a cDNA microarray that contained the SEQ ID NO:120-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, inflammation, and developmental disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-December 11, 1998 publications showing the state of the art on December 11, 1998. (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include more than three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on December 11, 1998 (and for several years prior to December 11, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Tang '129 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Tang '129 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:120-encoding polynucleotide probe] because a microarray that contained such a

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in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to December 11, 1998" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Tang '129 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pp. 33 and 36 of the Tang '129 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-December 11, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Tang '129 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Tang '129 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999).

In another pre-December 11, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

2. The Furness Declaration

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Tang '129 application on December 11, 1998 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ [11-15]). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. Furness Declaration at ¶ [11].)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Tang '129 application, the Wilkins article, and other related pre-December 1998 publications, persons skilled in the art on December 11, 1998 clearly would have understood the Tang '129 application to disclose the SEQ ID

> NO:120 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below. . . . (Furness Declaration, ¶10)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:120 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, inflammation, and developmental disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks,

due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that while the value in these databases is enhanced by their completeness, each sequence in them is independently valuable nonetheless.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and

disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide and polypeptide are not "specific and substantial" utilities. (Office Action at p. 3.) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide or Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a microarray, 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States

patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion) and the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

It is undisputed that known members of the signal peptide-containing protein family, including HSPP-120, are useful. Secretory proteins include hormones, cytokines, chemokines, and extracellular matrix molecules. These are the major factors involved in cellular signaling, immune defense, blood coagulation, and cell adhesion. The pharmacological usefulness of secretory proteins is recognized (See references of Toyoda et al. (Genome Research 13: 1728-

1736 (2003), and Ladunga et al. Current Opinion in Biotech. 11:13-18 (2000)). Toyoda et al. state that "secretory proteins are the most probable therapeutic agents, or targets, for antagonistic or agonistic therapy. Therefore, the development of efficient systems for identifying the genes encoding secretory proteins has been desired" (Toyoda et al., supra, page 1733). Ladunga et al. concur: "On a pharmaceutical perspective, secretory proteins, such as tissue-type plasminogen activator, erythropoietin, peptide hormones, digestive enzymes, and so on, account for the large majority of protein therapeutics" (Ladunga et al., supra, page 17). Thus, the claimed polypeptide is a member of the signal peptide-containing protein family, whose members indisputably are useful.

A recent Blast shows that the SEQ ID NO:120 polypeptide is 99.6% identical to the adenomatosis polyposis coli down-regulated 1 protein (DRAPC1)(see Exhibit A). DRAPC1 shows increased expression in colon tumors and may be useful as a diagnostic marker for colon cancer (Takahashi et al. (2002) Cancer Res. 62:5651-5656). This corroborates the statement on page 54 of the Specification that the SEQ ID NO:120 polypeptide and the polynucleotides encoding it may be useful in the diagnosis and treatment of cancer.

In the Office Action, the Patent Examiner takes the position that unless Appellants can identify which particular biological function within the class of signal peptide-containing proteins is possessed by HSPP-120, utility cannot be imputed. To demonstrate utility by membership in the class of signal peptide-containing proteins, the Examiner would require that all signal peptide-containing proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact

include predominately useless members, *e.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[2]

The Examiner addresses HSPP as if the general class in which it is included is not the signal peptide-containing protein family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the signal peptide-containing protein family does not. The signal peptide-containing protein family is sufficiently specific to rule out any reasonable possibility that HSPP would not also be useful like the other members of the family.

C. Because the uses of polynucleotides encoding HSPP in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The Examiner rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research,

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[2]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Bedilion and Furness Declarations. The claimed invention is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete.

Moreover, as discussed above in section II D., SEQ ID NO:120 is a signal peptide-containing protein. Therefore, the skilled artisan would have considered HSPP to be an important and valuable tool, in particular, for use in research on cancer, inflammation, and developmental disorders. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include uses such as diagnostic assays (e.g., pages 52-58), chromosomal markers (e.g., pages 58-59), ligand screening assays (e.g., pages 44 and 59-60), and drug screening (page 59-60).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 21-29, 31, 32, and 36-38 are rejected for allegedly failing to meet the requirements of 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims (Office Action pages 4-5). In particular, the Examiner alleges that the breadth of the claims is excessive with regard to Applicants claiming all polypeptide [sic] and polynucleotides which are less than the full-length of SEQ ID NO:120 or 254, including those which are at elast [sic] 90% identical to these molecules as well as biologically active or immunogenic fragments thereof" (Office Action, page 5). In addition, the breadth of claims 36-38 is allegedly excessive "since the claims read on all pharmaceutical compositions to treat all diseases associated with the decrease in any and all HSPP expression" (Office Action, page 5). Applicants traverse the rejection for at least the following reasons.

The first paragraph of 35 U.S.C. §112 requires that the Specification describe how to make and use the claimed subject matter. As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. Note that claims 21 and 31, for example, recite that the claimed polypeptides and polynucleotides comprise "**naturally occurring**" sequences. Through the process of natural selection, nature will have determined the appropriate sequences. Given the information provided by SEQ ID NO:254, one of skill in the art would be able to routinely obtain "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:254." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 30, lines 9-31, page 38, lines 6-18 and Example V at pages 64-68. Thus, one skilled in the art need not make and test vast numbers of polynucleotides. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides that already exist in nature.

The specification also describes the expression vectors into which the claimed polynucleotide fragments could be inserted, and the construction of fusion proteins (pages 34-40, Example IX at pages 69-70). Given this guidance, one of ordinary skill in the art would readily understand how to select and screen polynucleotides encoding fragments of SEQ ID NO:120 without any undue experimentation. Assays to detect secretion of HSPP and molecular interactions of HSPP are described in the specification, for example, at pages 71-72.

Members of the claimed genus of polynucleotide variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). The claimed genus of polynucleotide variants may be useful even if they encode defective polypeptides. For example, the variant polynucleotides could be used for the detection of sequences related to SEQ ID NO:254 (see the specification a page 17, line 9 through page 18, line 2, page 30, lines 9-31, page 53, lines 19-31) including variants that may be associated with disease states, such as the diseases listed on page 54, line 10, through page 55, line 56, line 25 of the specification. See the specification at, for example, pages 52-60 for disclosure of how to use the claimed sequences in diagnostic assays.

Since the claims of the instant application are drawn to naturally-occurring variants, it is not necessary to screen every conceivable variant which might be made using recombinant methods, as all that is claimed are those variant sequences which are found in nature. Given the

sequences of SEQ ID NO:120 and SEQ ID NO:254, one of ordinary skill in the art could readily identify naturally occurring polynucleotides having 90% identity to SEQ ID NO:120, polynucleotides having 90% identity to SEQ ID NO:254, and polynucleotides encoding a polypeptide having at least 90% identity to SEQ ID NO:120, using well known methods of sequence analysis, without any undue experimentation.

Claims 36-38 recite compositions comprising a polypeptide of claim 21 and a "pharmaceutically acceptable excipient." See the specification, for example, at pages 49-52 for guidance regarding the preparation of suitable pharmaceutical compositions. Claim 38 as currently pending does not read on "any and all HSPP expression." As amended, claim 38 reads as follows:

> A method for treating a disease or condition associated with decreased expression of a polypeptide of claim 21, comprising administering to a patient in need of such treatment a composition comprising a polypeptide of claim 21 and a pharmaceutically acceptable excipient.

As discussed above, the specification provides adequate guidance for a polypeptide having the sequence of SEQ ID NO:120, fragments of SEQ ID NO:120, and naturally-occurring variants having 90% identity to SEQ ID NO:120.

Further, the Examiner requires working examples. There is no such requirement under the law to provide "working examples." As set forth in *In re Borkowski,* 164 USPQ 642, 645 (CCPA 1970) (footnote omitted):

> However, as we have stated in a number of opinions, a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

See also M.P.E.P. 2164.02 as follows:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic"... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

Thus, there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to whether the specification provides a description of how to make what is claimed. The present specification provides the requisite description.

The skilled artisan would know how to use the claimed polynucleotides and polypeptides, for example in expression profiling, drug screening, disease diagnosis, or detection of related sequences as discussed above. Contrary to the standard set forth in *Marzocchi* and *Borkowski*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present specification would enable one to make and use the recited polynucleotides and polypeptides. Hence, a *prima facie* case for non-enablement has not been established. For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 21-29, 31, 32, and 36-38 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:120 and SEQ ID NO:254 are specifically disclosed in the application (see, for example, pages 11-14). Variants of SEQ ID NO:120 and SEQ ID NO:254 are described, for example, at page 13, lines 3-11, and page 14, lines 16-18. Incyte clones in which the nucleic acids encoding the human HSPP were first identified and libraries from which those clones were isolated are described, for example, at Tables 1 and 4 of the Specification. Chemical and structural features of SEQ ID NO:120 are described, for example, in Table 2. Given SEQ ID NO:120 and SEQ ID NO:254, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:120 having 90% sequence identity to SEQ ID NO:120 and naturally-occurring variants of SEQ ID NO:254 having 90% sequence identity to SEQ ID NO:254. Accordingly, the Specification provides an adequate written description of the recited polynucleotide and polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:120 and SEQ ID NO:254.

The Office Action has further asserted that the claims are not supported by an adequate written description because "the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:120 and SEQ ID NO:254 alone are insufficient to describe the genus" (Office Action, pages 6-7).

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional

characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides or polypeptides specifically in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claims 21 and 31 recite chemical structure to define the claimed genus:

> 21. An isolated polypeptide selected from the group consisting of: ...

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:120...

31. An isolated polynucleotide selected from the group consisting of: ...
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:254...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structures of SEQ ID NO:120 and SEQ ID NO:254. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to human signal peptide-containing proteins related to the amino acid sequence of SEQ ID NO:120. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as human signal peptide-containing proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:120. The "variant language" of the present claims recites, for example, polypeptides or polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:120" (note that SEQ ID NO:120 has 514 amino acid residues). This variation is far less than that of all potential human signal peptide-containing proteins related to SEQ ID NO:120, i.e., those human signal peptide-containing proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:120.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of December 11, 1998. Much has happened in the development of recombinant DNA technology in the 21 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:120 and SEQ ID NO:254, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide and polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:120 or SEQ ID NO:254. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides or polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action. Therefore, withdrawal of the rejections under U.S.C. § 112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 21-29, 31, 32, and 36-38 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 7). In particular, the Examiner states that it is not clear what is meant by the term "biologically active." Claim 21, has been amended to remove the biologically active fragment embodiment, which allegedly rendered dependent claims 22-29, 31, 32, and 36-38 indefinite. Therefore, the rejections with respect to these claims are moot.

In addition, the Examiner states that the "metes and bounds" of the term "HSPP" are allegedly unclear in claims 36-38. Applicants express confusion over the inclusion of claims 36 and 37 in the rejection, as the acronym HSPP appears only in claim 38 and not in claims 36 or 37. Claim 38 has been amended to remove the acronym; therefore, withdrawal of the rejections under U.S.C. § 112, second paragraph is respectfully requested.

Rejections under 35 U.S.C. § 102

Claim 21 and dependent claims 23 and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Blattner et al. (Office Action, page 7). Claim 21 c) has been

amended to recite an immunogenic fragment comprising at least **10 contiguous amino acid residues** of a polypeptide consisting of the amino acid sequence of SEQ ID NO:120. Support for this amendment is found in the specification, for example, at page 44, lines 12-19, which describes the production of antibodies in various hosts by immunization with "HSPP or with any fragment or oligopeptide thereof which has immunogenic properties," and at page 44, lines 20-22, which states that "[i]t is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HSPP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids." The polypeptide sequence disclosed by Blattner et al. does not contain 10 contiguous amino acid residues that match SEQ ID NO:120. Therefore, the reference does not disclose the claimed immunogenic fragments, and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claims 21, 23, 26-28, 32, 36, and 38 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Rosen et al. WO200055350 (Office Action, page 8). Applicants respectfully traverse the rejection.

The rejection under 35 U.S.C. § 102(e) is improper because the sequences SEQ ID NO:120 and SEQ ID NO:254 of the instant application were disclosed in the provisional application 60/112,129 and are entitled to the priority date of December 11, 1998. The priority date of WO200055350 is listed as March 12, 1999. Therefore, the claims are not anticipated by the reference of Rosen et al., and withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

Claims 21, 23, 32, and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bonaldo et al. Genome Res. 6:791-806 (1996) (Office Action, page 8). Applicants respectfully traverse the rejection.

The publication of Bonaldo et al. Genome Res. 6:791-806 (1996) is irrelevant since it does not disclose the sequences of the instant application, but rather describes methods to "facilitate gene discovery." The sequence BM715696, disclosed by Bonaldo et al., was first made available to the public at NCBI on February 28, 2002 (Please see Exhibit B). As mentioned above, the sequences of SEQ ID NO:120 and SEQ ID NO:254 are entitled to the priority date of December 11, 1998. Therefore, the claims are not anticipated by Bonaldo et al., and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 26-28 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over either Blattner et al. or Bonaldo et al each in view of Sibson et al. (WO 94/01548) (Office Action, page 9). This rejection is respectfully traversed for at least the following reasons.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02.

In the present case, the rejection of the claims under 35 U.S.C. § 103(a) is based on the allegation that the references of Blattner et al. and Bonaldo et al. disclose sequences that anticipate variants or fragments of SEQ ID NO:120 or SEQ ID NO:254. As mentioned above, the claims as currently pending are not anticipated by either reference. Since none of the references cited by the Examiner separately or in combination disclose or suggest the claimed sequences, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Respectfully submitted,

INCYTE CORPORATION

Date: September 30, 2003

Jenny Buchbinder, Ph.D.
Reg. No. 48,588
Direct Dial Telephone: (650) 843-7212

Date: September 30, 2003

James M. Verna, Ph.D.
Reg. No. 33,287
Direct Dial Telephone: (650) 845 -5415

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886